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# Pre-radiotherapy dental extractions and osteoradionecrosis: a retrospective analysis and cross-sectional study on quality of life

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## Abstract

### Background

Radiotherapy (RT) is widely utilised for the management of head and neck malignancies, and presents a number of morbidities. One of the most feared late sequelae is osteoradionecrosis of the jaws (ORN). Many risk factors for ORN exist including radiation delivery, dose and fractionation, tumour location, smoking and alcohol use, general health and nutrition status, oral health and oral hygiene. There also exist triggers that increase the likelihood of ORN developing, such as dental extractions, surgery or poor fitting prostheses as well as any residual foci of infection.

In order to prevent post-radiotherapy dental extractions and therefore reduce the risk of developing ORN, it has been advocated that dental extractions are performed prior to radiotherapy. However, there is contention that such pre-RT extractions may actually increase the risk of developing ORN. Newer RT technologies and techniques deliver a lower dose to the jaws and critical structures, and coupled with improved oral hygiene methods radiotherapy related dental disease can be limited and the chances of retaining a functioning dentition greatly improved.

Head and neck cancer diagnosis and treatment places a heavy stress on patients and impacts their quality of life. Independent of a cancer diagnosis, edentulism is associated with reduced oral function and health related quality of life.

### Aims

1. To determine if pre-radiotherapy dental extractions are associated with an increased risk of developing ORN.
2. To determine if pre-radiotherapy dental extractions are associated with a reduced health related quality of life.

### Methods

Regional and site-specific ethics approval was obtained. Patients over the age of 18 who were treated with radiotherapy for oropharyngeal cancer at two tertiary Australian hospitals between 2005 and 2011 were invited to participate in the study. All participants were presented to a head and neck MDT and underwent pre-radiotherapy dental assessment. Demographics and retrospective analysis of the treatment details of the 190 consenting participants were recorded. Participants completed questionnaires regarding their oral

hygiene, dental extractions and dental experience. A diagnosis of osteoradionecrosis was confirmed. Participants also returned two health-related quality of life forms, the OHIP-14 and FACT-Head and Neck, which were utilised according to their guidelines. The FACT-Head and Neck results were used to calculate subset scores and the outcome scores FACT-G, FACT-TOI and Fact Total. Multivariate logistic regression was performed.

**Results**

190 participants were recorded, of whom the majority were male (82.6%) and underwent concurrent chemotherapy and radiotherapy (87.9%) with a mean dose of 68 Gray. 67.9% underwent pre-radiotherapy dental extractions with a mean of 5.1 teeth. Mandibular teeth were favoured 1.7:1. Current smokers were more likely to undergo extractions ($p=0.02$). No teeth were extracted during radiotherapy. 30 participants underwent post-radiotherapy extractions, 20 of which after already receiving pre-radiotherapy extractions. The mean number of teeth extracted was 0.85 and did not favour either arch.

29 participant (15.3%) developed ORN in the follow up period, favouring the mandible (89.6%).

Pre-radiotherapy dental extractions were associated with the development of ORN (OR 3.19, $p<0.05$). The number of extractions was associated with an increased risk of ORN (OR 1.13 per extraction, $p<0.05$). Post radiotherapy extractions were associated with a similar odds ratio but were not statistically significant. Current and ex-smokers were at an increased risk of developing ORN compared with non-smokers, as well as p16 negative status.

The range of quality of life outcome scores were broad and nearly encompassed the entire possible scores. OHIP-14 scores showed a statistically significant worse QoL for females, p16 negative status and stepwise in smoking status from current to ex to non-smokers. More than 8 pre-radiotherapy extractions, pre-radiotherapy full clearance and the development of ORN also produced statistically significant associations with a worse QoL. The only measure associated with an improved QoL was current excellent dental hygiene.

FACT-Head and Neck showed that smoking status was associated with a global reduction in QoL across the subset scores emotional well being, social well being, functional well being, physical well being and head and neck specific scores. P16 negative cases were

associated with reduced QoL in the social well being and head and neck specific domains. Female gender was associated with reduced QoL in the emotional well being domain.

**Conclusion**

Pre-radiotherapy dental extractions do not appear to reduce the risk of ORN, and may in fact increase the risk. Pre-radiotherapy dental extractions do not increase health related quality of life, and may in fact worsen it.

**Declaration by author**

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my research higher degree candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

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## Publications during candidature

### *Peer-Reviewed Journal Articles*

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| Contributor | Statement of contribution |
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| Dr Nicholas Beech | Wrote and edited paper, 80%. |
| Dr Stephen Robinson | Wrote sections 'Pre-radiotherapy dental management: restorations' and 'Post-radiotherapy management: restorative considerations', 20%. |
| A/Prof Sandro Porceddu | Designed, reviewed and edited paper, 50%. |
| A/Prof Martin Batstone | Original idea and design 100%. Reviewed and edited paper, 50%. |

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| A/Prof Sandro Porceddu | Designed, reviewed and edited paper, 50%. |
| A/Prof Martin Batstone | Original idea and study design 100%. Reviewed and edited paper, 50%. |

**Contributions by others to the thesis**

Dr Robert Ware, University of Queensland School of Population Health provided statistical support and estimations.
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None.

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**Keywords**

Radiotherapy, dental extractions, osteoradionecrosis, quality of life, head and neck cancer

**Australian and New Zealand Standard Research Classifications (ANZSRC)**

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**Table of Contents**

## List of Figures & Tables

**List of Abbreviations used in the thesis**

Exo = dental extractions
FACIT = functional assessment of chronic illness therapy
FACT-H&N = functional assessment of cancer therapy – head and neck
GIC = glass ionomer cement
HNC = head and neck cancer
HPV = Human Papilloma Virus
IMRT =intensity-modulated radiotherapy
ISOO = International Society of Oral Oncology
MASCC = Multinational Association of Supportive Care in Cancer
MDT = multidisciplinary team
MMP = matrix metalloproteinases
OHI = oral hygiene information
OHIP-14 = oral health impact profile -14
OPC = oropharyngeal candidiasis
OR = odds ratio
ORN = osteoradionecrosis
P16 = Human Papilloma Virus type 16
Post-RT = post-radiotherapy
Pre-RT = pre-radiotherapy
PRP = platelet-rich plasma
RMGIC = resin modified glass ionomer cement
RT = radiation therapy
WHO = world health organisation

# Introduction

## Dental Management of the irradiated patient

Head and Neck Cancer (HNC) is often treated with radiotherapy (RT), a method that utilises ionizing radiation to exert therapeutic effect by semi-selectively targeting rapidly dividing cancer cells. RT produces a number of undesirable effects through the damage of normal cells. One of the most feared late complications of RT is Osteoradionecrosis (ORN) of the jaws. A number of risk factors exist for ORN, and although spontaneous ORN is possible, the condition is often associated with a dentoalveolar trigger event, such as dental extractions [1, 2]. RT often results in hyposalivation and can lead to rapidly progressive radiation caries, thus leading to the need for multiple extractions [3]. As such, patients planned for radiotherapy need to have a comprehensive dental assessment prior to treatment commencing, as well as close recall and monitoring. In the first chapter of this thesis, a review of the literature will provide contemporary management of the irradiated patient prior to, during and following their treatment.

## Radiotherapy-associated dental extractions and osteoradionecrosis

Following radiotherapy, minimisation of dentoalveolar trigger events is key in reducing the incidence of ORN. Traditionally, these trigger events were post-radiotherapy dental extractions, and clinicians advocated that prophylactic removal of teeth in radiation fields would eliminate post-radiotherapy dental complications and thus the need for extractions, with the ultimate goal being the reduce the incidence of ORN [4]. Recently, authors have begun to investigate pre-radiotherapy trigger events as being related to ORN [4]. As there have been no randomised controlled trials investigating radiotherapy-associated dental extractions it is currently unclear when the ideal timing for extractions are [5]. Advances in both preventative dental management and newer radiation techniques reducing the radiotherapy dose to the tooth bearing alveolus and major salivary glands are likely to result in increased tooth retention, decreased need for post-radiotherapy extractions and decreased incidences of ORN[6]. It is hypothesised that such pre-radiotherapy dental extractions are possibly not necessary and may in fact be harmful. The second chapter of this thesis will investigate whether dental extractions included as part of the pre-radiotherapy treatment plan are associated with an increased risk of post-radiotherapy ORN.

**Radiotherapy-associated dental extractions and health-related quality of life**

Head and neck cancer diagnosis places a significant stress on patients and their social supports. Additionally, RT as a treatment modality is highly morbid, with impacts on speech, mastication, appearance and social interaction [7]. While treatments are designed to reduce disease and prolong survival, there has been a recent emphasis on the quality of life effects of treatment [8, 9]. A healthy dentition may appear secondary to prolonged survival, however it should not be disregarded as an important factor in quality of life, as the stomatognathic system is central in aesthetics, communication and diet. As such, any plan for dental extractions must weigh the risks and benefits of extraction, looking beyond merely the absence of disease and encompassing the psychosocial wellness of the individual. It is understood that dental extractions impair quality of life in a general population[10], however there are currently no studies investigating how dental extractions affect survivors of head and neck cancer. In the third chapter, this thesis will investigate the effects of radiotherapy-associated dental extractions and health-related quality of life.

## Chapter 1

## Dental management of patients irradiated for head and neck cancer

*Australian Dental Journal (2014).*

**Abstract**

Patients undergoing radiation therapy as either primary, adjuvant, combination therapy or palliative management of head and neck malignancies are prone to a range of dental complications. Strategies for prevention and management of such complications may be controversial. This article aims to highlight the current understanding and management of the dental needs for patients before, during and after radiation therapy.

### Introduction

Head and neck cancers (HNC) are often treated with radiation therapy (RT), a technique that utilizes ionising radiation and exerts therapeutic effect by semi-selectively damaging the genetic material of vulnerable malignant cells, either directly or through the production of free radicals, resulting in cell death.

Adverse effects of RT arise by the same mechanism damaging normal cells, especially those that are rapidly dividing, or otherwise less capable of repairing radiation induced damage [11]. In the oral cavity these can be cells of the mucous membrane, underlying soft tissue, tooth, periosteum, bone, glands and vasculature resulting in specific radiation syndromes. Such syndromes include xerostomia and dysgeusia from salivary gland damage, mucositis from epithelial damage, pathological alterations in the normal flora alterations, radiation caries, reduced mouth opening from changes in collagen structure and osteoradionecrosis of the jaw (ORN) from reduced bone healing capacity [12-16].

Management of oral health is especially important for the HNC patient, as oral complications are common both during and after radiation. For example, xerostomia may affect up to 90% of patients undergoing radiotherapy; mucositis more than 60%; candidiasis more than 40%; post-radiotherapy dental decay more than 50%[17] and osteoradionecrosis up to 15% [13, 14, 18, 19].

While the majority of oral complications are unavoidable consequences of ionizing radiation (deterministic), some are preventable [6]. The incidence of some complications is associated with treatment factors, such as in the case of osteoradionecrosis and dental extractions [4, 18, 20-22]. As oral complications are common, potentially preventable and

have iatrogenic factors, it is essential that those working with HNC patients be aware of the prevention and management of radiotherapy-related oral complications.

In this article we aim to highlight the current understanding and management of the dental needs for patients who have or will undergo radiation therapy.

**Pre-Radiotherapy Dental Assessment**

The benefit of a Multi-Disciplinary Team (MDT) approach to assessing, diagnosing and managing head and neck cancer patients is widely acknowledged and as such, every patient with head and neck cancer should be managed in this environment[23]. Given the oral and dental implications related to treatment, a dental practitioner with experience in HNC should be included at the minimum. An expanded dental team would include specialists in restoration and rehabilitation as well as health practitioners to educate and teach preventative dental care.

At our centre, every patient receives a thorough pre-radiotherapy assessment with an experienced general dentist who gives preventative advice and performs necessary extractions and fillings. We believe the final oral rehabilitation should be considered at the beginning of treatment and as such patients are seen by a specialist prosthodontist. The assessment includes consideration of the diagnosis, prognosis, proposed treatment, individual patient factors and pre-existing oral health. Immediate management involves extractions of unrestorable teeth or those with gross periodontal disease prior to treatment irrespective of fields. All healthy teeth as well as deeply impacted teeth without pathology are left in situ. Extractions are undertaken with as little trauma as possible and minimal flap surgery.

Depending on financial eligibility patients are then referred back to their general dentist with a thorough plan or continued to be seen at the clinic. In general, we advise routine three-monthly checkups, daily fluoride and bicarbonate rinses and restorations as required.

General dental practitioners should be aware of their local MDT and clinics where HNC patients are seen and refer patients who present with complications.

The cancer diagnosis should include tumour type and staging, location within the oral cavity and proximity or involvement of adjacent structures. Human Papilloma Virus (HPV) status is an important prognostic factor[24], however a review of the literature does not reveal an increased risk of radiotherapy associated complications such as ORN, mucositis, candidiasis or xerostomia.

Important treatment factors include the anticipated radiation dose, field size and location. Specific areas receiving doses over 60 Gray should be flagged as higher risk for complications, especially if the major salivary glands are included. The use of surgery or chemotherapy should be known. It is practical to have a rough timetable for treatment and follow up appointments.

A full medical and dental history should be taken, as with all patients. Factors likely to increase the risk of oral complications should be noted, and the opportunity should be taken to discuss risk factor modification, such as smoking and alcohol cessation.

The patient should be assessed for motivation, and whether they are able to manage expected dental hygiene regimens. Motivation is of paramount importance but difficult to assess. Current dental hygiene habits and prior engagement with dental professionals may be of some use. If there are significant concerns with motivation, additional appointments with an experience hygienist could help prevent complications.

Finally the oral cavity itself should be examined, and relevant radiographic images obtained, such as bitewings and periapicals if indicated. The patient's general dentition, as well as a tooth-by-tooth assessment should be recorded. If the patient wears dentures they should be advised to avoid using them until treatment is completed.

**Pre-Radiotherapy Dental Management: Restorations**

The general goals of dental care are no different for HNC patients, that being a functional, aesthetic dentition. However, special attention should be given to avoid using patient time on extensive treatments. The goals are made difficult in the HNC population for a number of reasons. Firstly, the time interval between decision to treat and the initiation of radiotherapy is often short, meaning treatment must be prompt. Secondly, recently diagnosed HNC patients have a relatively high prevalence of dental disease[13, 25], with one study showing only 11% of patients did not require pre-radiotherapy dental care[26]

and up to 50% requiring at least one extraction [13]. Scaling, prophylaxis and fluoride application should be performed and where simple restorations are required these should be carried out before radiotherapy begins. If time does not permit definitive restoration, provisional restoration with a glass ionomer cement is often appropriate. As amalgam may cause back-scatter and subsequent local mucositis[27], they are therefore generally avoided. The presence of sharp cusps or restorations is an important issue for the HNC patient, as these may cause considerable trauma to the vulnerable irradiated soft tissues. This is often completely avoidable and can be prevented with simple smoothing or repair. Impressions should be taken for study models and the fabrication of soft mouth guards or medicament carrying trays at a later date is also prudent. If the patient wears dentures, these should be checked to ensure they are well-fitting, and not at risk of causing ulceration.

**Pre-Radiotherapy Dental Management: Extractions**

The extraction of teeth pre-radiotherapy is a controversial topic. The assumption that all or most teeth should be extracted prior to radiotherapy is based on the belief that radiotherapy leads to untreatable periodontal disease even in healthy teeth, and that post-radiotherapy extractions lead to higher rates of complications such as osteoradionecrosis of the jaw, in addition to being technically more difficult[4].

The criteria used by Ben-David et al[6] are a useful guide for extractions: “teeth with non-restorable caries, or caries that extend to the gum line, teeth with large, compromised restorations with significant periodontal attachment loss (pocketing >5mm), and those with severe erosion or abrasion are extracted if they are in parts of the jaws expected to receive a high dose. Teeth residing in the anterior mandible are not considered for extraction unless the primary tumor was in the oral cavity. Decisions about extraction were significantly affected by the patient’s competence and interest in performing meticulous oral hygiene, and by past history of dental service usage”. Other factors to be taken into consideration would include unopposed teeth that would cause trauma to the gums.

There is inconsistent evidence surrounding pre-radiotherapy extractions and their link to the development or ORN. Some studies have shown that the lack of pre-radiotherapy extractions presents a risk factor for ORN[28], while other studies have found that pre-radiotherapy extractions are not beneficial in reducing rates of ORN regardless of tooth condition [20] and may actually increase the overall risk of ORN [4, 18, 21, 22].

If extractions are performed, it is important to allow sufficient healing time prior to the commencement of radiotherapy but not to unduly delay it. An accepted interval between extractions and radiotherapy is ten days to three weeks[4, 6, 29, 30].

**Dental Management During Radiotherapy: Mucositis**

The oral basal epithelium has a rapid cellular turnover and is therefore at higher risk of radiation damage[31]. Cell death and the inability of the mucosa to repair lead to oral mucositis (OM), typically presenting as atrophy, swelling, erythema, ulceration and pseudomembrane formation, frequently accompanied by colonization with gram-negative organisms and candida species. OM can cause considerable pain, as well as functional difficulties including eating, drinking and speech [15, 32, 33]. In some cases, nasogastric or PEG feeding may be required.

In HNC patients receiving RT, up to 80% of patients may develop mucositis usually occurring after 7-10 days of treatment, and potentially lasting for months [32, 34]. The soft palate is affected most severely, followed by the hypopharynx, floor of mouth, cheeks, tongue and lips[15]. Grading scales such as the World Health Organisation (WHO) oral toxicity scale adapted for oral mucositis are useful; Grade 0 is no oral mucositis and Grade 4 is where the patient has ulcers and alimentation is not possible[35].

Methods used to prevent and treat mucositis include good dental hygiene such as frequent brushing with a soft, regularly replaced toothbrush, regular flossing, four-hourly non-medicated oral rinses, adequate hydration and the avoidance of oral irritants such as alcohol and tobacco. Symptomatic treatment includes tooth mousse and topical barrier gels. The Multinational Association of Supportive Care in Cancer (MASCC) and International Society of Oral Oncology (ISOO) updated guidelines recommend that sucralfate, chlorhexidine and antimicrobial lozenges not be used for the prevention of radiotherapy induced oral mucositis, but do state that benzydamine has a role for patient receiving moderate dose RT [36]. Other agents that have been investigated include aloe vera gels and honey products, which may be beneficial for some patients [37, 38]

In patients with metal fillings, the use of dental-protective stents to prevent scattering may reduce the incidence of local mucositis [6]. We recommend that patients receive appropriate analgaesia for their pain, and are screened by a dietician to assess their oral intake.

**Dental Management During Radiotherapy: Oropharyngeal Candidiasis**

Oropharyngeal candidiasis (OPC) is caused by both albicans (>80%) and non-albicans species, and is a frequent infection after radiation therapy to the head and neck[15, 39]. Although candida is a normal oral commensal that occasionally causes infection in healthy patients, radiotherapy related hyposalivation alters the oropharyngeal environment and significantly increases the risk of colonization and infection. While it may be regarded as benign, it can be a significant cause for morbidity and decreased quality of life.

OPC typically affects the tongue, oral cavity and labial commisure, and presents in three forms; pseudomembranous, erythematous/atrophic and cheilitis [39]. The usual appearance is that of removable white lesions overlying an erythematous and atrophic patch. Symptoms may be absent or include burning pain, difficulty swallowing, dysgeusia, and halitosis.

OPC is treated when symptomatic and focuses on local therapy unless the presentation is severe, disseminated candidiasis is suspected, the patient is high risk (i.e. immunosuppressed) or fails to respond to local methods. Prevention is through regular dental hygiene, saliva substitutes and smoking and alcohol cessation. First line treatment includes topical miconazole, fluconazole or nystatin, available in several forms such as creams, suspensions or lozenges. When systemic therapy is indicated, the first line drug is oral fluconazole.

**Dental Management During Radiotherapy: Xerostomia**

Radiation damage to the salivary glands, especially the parotids, results in gland dysfunction through cell death and fibrosis. The result is hyposalivation and increased salivary viscosity experienced as xerostomia. Xerostomia causes functional issues within the oral cavity, affecting speech and taste, as well as causing chewing and swallowing difficulties. Furthermore, hyposalivation increases the risk of developing oral infections such as candidiasis, gingivitis and acute suppurative sialadenitis, as well as increasing the risk of developing caries[12].

The incidence of xerostomia is related to the tumour location and technique used to deliver radiotherapy, as well as the dose delivered. Even small doses can result in a large proportion of glandular destruction. Newer radiotherapy techniques such as intensity-

modulated radiotherapy (IMRT) avoid larger radiation doses to the parotids, and retain greater function[40].

There are a number of methods that propose to reduce xerostomia, such as amifostine, intra-glandular botulinum therapy and alpha-tocopherol, however these may not produce the desired effect. Currently systemic treatments for the prevention of xerostomia are only used in a research setting[12].

Management of xerostomia begins with the same methods as all other radiotherapy syndromes- good oral hygiene. This reduces the severity of xerostomia as well as preventing secondary complications such as caries. Salivary substitutes should be used for symptom relief, as well as regular non-medicated oral rinses. Sialogogues such as chewing gum and the cholinergic agonist pilocarpine can also be used for relief of symptoms and may offer some dental protection, however adverse effects of pilocarpine such as sweating, diarrhoea and bronchospasm may limit its use in some people[12, 34].

**Dental Management During Radiotherapy: Emergencies**

A thorough pre-treatment assessment and management of incipient dental conditions should ideally prevent dental emergencies during radiotherapy.
Cessation of radiotherapy treatment is to be avoided as delays reduce treatment effectiveness and therefore survival[41].

Before treating, contact should be made with the treating radiation oncologist and the nature of the condition discussed. Acute onset of toothache may be successfully managed with standard restorative or endodontic techniques, although increased difficulty should be anticipated due to radiation mucositis, general discomfort and limited mouth opening.

Dental extractions are a troublesome issue, and due to technical difficulty and increased complication there should be a low threshold for tertiary referral, especially if the teeth fall within the radiation field. If indicated, they should be performed with minimal trauma by an appropriate specialist.

**Post-Radiotherapy Management: Hygiene and Radiation Caries**

Following radiation, chemical and microbial changes in the oral cavity result in a cariogenic environment[34]. Over half of all patients will demonstrate dental deterioration over time

with an incidence risk of 6% per month[17]. Radiation caries occurs even in teeth not exposed to radiation, and if not managed can progress to full dental loss over a period of as little as three years[42].

Incidence is related to radiotherapy dose, with an odds increase of 2-3 at 30-60 Gy, and 10 at over 60Gy. The proposed mechanism is that the salivary glands withstand doses up to 30Gy and sustain maximal damage between 30-60Gy. The additional risk is due to direct radiation effects on the tooth structure, which weakens dentin-enamel bonds and results in shear fracturing[17].

Radiation caries occur at different locations than in common dental decay. The sites most affected post-radiotherapy are the labial surfaces of the cervical, cuspal and incisor areas. These areas receive compression, torsion and shearing forces and are the regions most resistant to caries in non-irradiated patients[17, 34].
Prevention is key. Use of fluoride in medicament carrier trays dramatically reduces the risk of dental deterioration, and prescription fluoride should be used at least once daily. In one study, each additional daily use of fluoride per week resulted in a 14% reduction in moderate or severe dental deterioration[17].
Additional preventative techniques include dental hygiene measures such as regular rinses, brushing, flossing and the management of xerostomia. Rinses should be either non-acidic fluoride preparations or bicarbonate preparations, and brushing and flossing should be gentle and thorough.

**Post-Radiotherapy Management: Restorative Considerations**

Restorative management of radiation caries can be challenging and may be compounded by limited access due to trismus or scarring and poor moisture control as a result of marginal gingivitis. The restorative dentist must consider these challenges, along with an altered dental substrate and a hostile oral environment when selecting restorative materials. Ideal properties would include resistance to recurrent caries, adhesion to tooth structure, durability, acceptable aesthetics and ease of handling. None of the currently available materials meet this standard and there is only limited evidence in the literature to guide material choice.

Radiation induced changes in enamel and dentine may compromise bonding of adhesive materials[43] though the extent and mechanism of such changes are controversial. Some

studies have indicated altered prismatic structure within enamel and reduced physical properties [44, 45] while others have failed to demonstrate significant enamel changes. Water molecules in dentine undergo radiolysis releasing free radicals which denature collagen and reduce its mechanical properties[46]. Free radicals can interfere with polymerization of resins while irradiation also activates enzymes including matrix metalloproteinases (MMPs) within dentine, which have been shown to hydrolyse dentine bonding agents[47]. Consequently, loss of retention or development of recurrent caries around composite restorations is often observed[48].

Glass ionomers cements (GICs) lack strength however they do enjoy simpler bonding procedures and chemical adhesion as well as fluoride release and reuptake, which may reduce recurrent caries, even if the material is subsequently lost[49]. De Moor et al[48] demonstrated significantly less recurrent caries around Class V GICs compared to resin composites in irradiated patients. This difference was particularly marked when fluoride use was low. Resin Modified Glass Ionomers (RMGICs) have improved structural and marginal integrity, similar recurrent caries rates and greater resistance to acid erosion so may be good alternatives to conventional GICs. What evidence is available suggests that where caries risk is high or patient compliance is poor, GICs (conventional or resin modified) are the materials of choice.

Extensive caries increases the risk of pulpal involvement. Irradiation may alter pulp vascularity and therefore its capacity for repair[50]. Within radiation fields, where caries involves the pulp, endodontic treatment is generally preferred to extraction. Even teeth deemed un-restorable may be root filled and sealed to control symptoms and infection while minimizing the risk of ORN. Trismus and poor access can however complicate root canal therapy. Rubber dam placement may be challenging and a lack of inter-occlusal space may prevent ideal canal access. Cutting access cavities through the labial or incisal aspects or decoronating grossly carious teeth may be an acceptable compromise. Success rates of endodontics in irradiated patients have received limited attention in the literature but seem to be acceptable[51].

Crown and bridgework is generally avoided in xerostomic patients. Unless compliance with preventive advice is optimal, restoration margins will be vulnerable to recurrent caries. In compliant patients with a stable dentition, simple indirect restorations may be considered. Margins should be kept supra-gingival and hygienic design is essential. Craddock[52]

demonstrated that fixed prosthodontic rehabilitation can prove successful over several years.

Generally removable prostheses should be avoided in irradiated partially dentate patients unless they are essential for aesthetics or function. It is accepted that partial dentures compromise plaque control[53] and that a shortened dental arch is often adequate for function and aesthetics[54]. Where they are unavoidable their design should be hygienic and patients must be counseled regarding the risks and strongly encouraged to maintain impeccable oral and denture hygiene. Care should also be exercised when providing dentures for patients who have undergone pre-radiotherapy extractions. Particularly where dentures are tissue borne, there is a risk of trauma and ORN careful clinical technique should be supplemented with patient education and regular recall. Conventionally, denture provision has delayed for 12 months or more after completion of radiation to allow healing and ridge remodelling. This has been questioned in recent years with one study showing similar complication rates whether dentures were inserted within 6 months or delayed by up to a year[55].

**Post-Radiotherapy Management: Extractions and Osteoradionecrosis**

Osteoradionecrosis is a serious and typically late complication following radiation therapy to the head and neck whereby irradiated bone is exposed and undergoes necrosis. The exact pathophysiology is unclear and a number of proposed mechanisms exist, from Marx's 'three Hs' theory through to the current fibroatrophic theory[56].

A great number of staging systems exist for ORN *(Table 1)*[57]. One of the first methods was Marx's system where stage was based on response to the Wilford Hall hyperbaric oxygen protocol, with potential to directly enter a higher stage if the initial presentation was severe[58]. More contemporary systems such as Kagan and Schwartz's three stages classify ORN based on clinical presentation, and then treatment is decided according to the stage[1]. A simple system is presented by Notani et al based on clinical presentation[59]. Staging systems have focused on the mandible, as the maxilla is unlikely to develop ORN.

**Table 1. Selected staging systems for ORN**

| | |
|---|---|
| Marx 1983 | |
| I | Initial cases of ORN and those responding to 30 HBO treatments |
| II | Failure to respond to initial 30 HBO treatments and/or response to alveolar sequestrectomy |
| III | Failure to respond to 60 HBO treatments and sequestrectomy, or initial presentation either with pathologic fracture, orocutaneous fistula or radiographic evidence of resorption to the inferior border |
| Kagan and Schwartz 2002 | |
| I | Superficial involvement of the mandibular cortex only with minimal soft tissue ulceration |
| II | Localized involvement of the mandibular cortex and underlying medullary bone |
| II a | As for II, with minimal soft tissue ulceration |
| II b | As for II, with soft tissue necrosis, including orocutaneous fistula |
| III | Diffuse involvement of the mandible. Full thickness necrosis including the lower border |
| III a | As for III, with minimal soft tissue ulceration |
| III b | As for III, with soft tissue necrosis, including orocutaneous fistula |
| Notani *et al.* 2003 | |
| I | ORN confined to the alveolar bone |
| II | ORN confined to the alveolar bone and/or the mandible above the mandibular alveolar canal |
| III | ORN extended to the mandible under the level of the mandibular alveolar canal and ORN with a skin fistular and/or pathological fracture |

*Table 1.1 Selected staging systems for ORN*

Preventative measures are vital to avoid the need for dental intervention such as extractions and may have led to a significant decline in rates of ORN over the last few decades[60]. However, even with adequate care, the extraction of diseased teeth may become inevitable. A minimal trauma technique is especially indicated in the irradiated patient and therefore experienced clinicians should perform the procedure. In addition, investigators have proposed that the number of teeth removed in a single session should be limited, and specific local anaesthetics should be avoided, however data for these recommendations appear to be lacking and should be further investigated before they have an impact on clinical practice [3, 61, 62].

In order to further reduce the rates of ORN, clinicians have used prophylactic antibiotics, platelet-rich plasma (PRP) and steroids in order to reduce osteoradionecrosis, however none of these methods have resulted in a consistent and significant reduction in the rates of ORN and are not without their own risks. The use of prophylactic and therapeutic HBO for ORN is controversial.

In general we advise that General Dental Practitioners consider endodontic treatment first, to avoid extractions. Should this fail or if extractions become necessary, General Dentists can safely extract teeth out of field or in fields less than 50 Gray with primary closure of the socket. Teeth in fields greater than 50 Gray should be referred to the treating Oral and Maxillofacial Surgery department.

**Post-Radiotherapy Management: ORN and Hyperbaric Oxygen**

The theoretical benefit of HBO links in with one of the proposed mechanisms of osteoradionecrosis, where ORN is the result of 'hypoxia, hypocellularity and hypovascularity'. HBO promotes angiogenesis, and therefore should reduce ORN [16]. The standard Marx 30/10 HBO protocol consists of 30 treatments at 2.4 atmospheres for 90 minutes prior to extraction, followed by 10 treatments of 90 minutes post-extraction.

A number of criticisms of HBO for the prevention and treatment of ORN exist. A recent systematic review found no benefit when prophylactic HBO is used in associated with extractions [63], and another pooled the overall complication rate for patients undergoing HBO, revealing a complication incidence of about 7.8%, including minor symptoms through to seizures, stroke and death[4, 64]. The only randomised, controlled trial was conducted by Annane et al in 2004 and was stopped due to potentially worse outcomes in the HBO group[65]. Additional criticism is that studies of prophylactic HBO have been few in number, contain a small sample size and are generally dissimilar [4, 66].

These criticisms must be contrasted with the positive findings from a number of studies, including pooled data. A recent systematic review showed weak evidence that HBO reduced the rate of post-radiotherapy extraction related ORN from 7% to 4%[61], a Cochrane review published in 2012 showed some benefit for therapeutic HBO in regards to mucosal cover and prevention of wound dehiscence but concluded that more and better quality data was needed[67]. It is promising therefore, that larger trials are underway[68].

**Post-Radiotherapy Management: ORN, Antibiotics and PRP**

The use of antibiotics has been advocated for the prevention of ORN, which, although unproven, has been theorized to be an infectious process, or at least process in which bacterial play a role [4]. A questionnaire of practitioners revealed there was no consensus on the type or duration of antibiotics used, although a general trend was to use antibiotics that cover both aerobic and anaerobic bacteria[69]. There is weak evidence to suggest that the use of antibiotics in general confers a 1% absolute risk reduction in ORN compared to no antibiotics. Despite only weak evidence, prophylactic antibiotic use is still common following extractions[61]. The authors do not encourage use of antibiotics where there is no infection.

Autologous PRP has been promoted for various applications, including bone grafts and various head and neck procedures. The theoretical mechanism of prophylaxis is that a number of growth factors present in platelets, including PDGF, TGFβ and VEGF, result in improved healing and better outcomes. A recent randomized controlled trial showed no relationship between PRP use and development of ORN or improved pain scores[18]. It is reasonable to conclude that the use of PRP should be questioned in this setting.

**Post-Radiotherapy Management: ORN, Pentoxyfylline and Tocopherol**

Pentoxyfylline, a phosphodiesterase inhibitor used in peripheral vascular disease, and tocopherol (vitamin E) are used with or without the bisphosphonate clodronate as a novel combination therapy for the management of ORN. Current studies show impressive outcomes with these drugs, such as a study where 54 patients with refractory ORN all experienced full recovery in a median of nine months[70-72]. Similar studies have not all shown the same outcomes, and as such more research is needed in this field[73].

**Post-Radiotherapy Management: Treatment of Osteoradionecrosis**

For the patient who develops ORN, prompt referral should be made to a tertiary maxillofacial unit for further management. Treatment of ORN ranges from conservative methods such as saline rinses through to debridement, sequestrectomy, resection and free flaps, with or without the use of adjuncts such as HBO or pentoxyphylline, tocopherol and clodronate [70-72, 74, 75].

**Follow-up and Discharge**

Follow up should be performed by a head and neck cancer multidisciplinary team at units approved for the diagnosis and management of head and neck cancers. Discharge back to the community dentist is appropriate if the patient has successfully completed all treatments and has no active complications. The community dentist accepting the patient should have an understanding of the dental needs of irradiated patients and a knowledge of when to re-refer.

From a dental perspective, regular dental follow up should be every three months. This ensures education is reinforced and any dental issues are addressed early. The dental consultation should review the treatment course and cover any history of complications. The patient’s dental hygiene and regular dental routine should be assessed, and any opportunities for education should be taken advantage of. The patient should then be

examined and any necessary management enacted. Finally, it is of great value to the rest of the team to receive letters detailing the patient's dental visits and opinions of the dental practitioner.

**Conclusions**

The management of the patient irradiated for head and neck cancers is an excellent opportunity for preventative care. There are a number of proposed adjunct therapies for the prevention and treatment of complications, however few of these are supported by strong evidence. Further research is necessary in multiple areas, in particular pre-radiotherapy extractions and the use of hyperbaric oxygen.

## Chapter 2:

## Radiotherapy-associated dental extractions and osteoradionecrosis

*Head and Neck (2016)*

### Introduction

Radiotherapy (RT) is widely utilised for the management of head and neck malignancy and is associated with significant morbidity, manifest during treatment and often persisting permanently. One of the most feared late sequelae is osteoradionecrosis of the jaws (ORN), a condition of impaired wound healing characterised by non-vital bone in radiation fields not related to tumour recurrence[1]. Many risk factors for ORN exist including radiation delivery, dose and fractionation, tumour location, smoking and alcohol use, general health and nutrition status, oral health and oral hygiene. There also exist triggers that increase the likelihood of ORN developing, such as dental extractions, dental implants, surgery or poor fitting prostheses [2] as well as any residual foci of infection[76].

In order to minimise the risk of ORN and other radiation-related negative effects on the oral cavity, it is recommended that all patients are seen by a dental clinician prior to the commencement of treatment. At this visit, the oral status is assessed and appropriate dental treatments are completed. The dental needs of patients diagnosed with HNC are often quite high, and patients frequently present with periodontal disease and caries [13].

At the pre-RT dental review, extractions are often performed. The timing of such dental extractions is important to note, as controversy exists regarding best practice for extraction [4]. Some authors in the past have advocated various regimens in order to prevent dental extraction in the post-radiation period. The rationale behind these regimens is usually as follows: that chances of needing dental extraction in the post-radiation period have traditionally been higher due to altered oral function eg hyposalivation, radiation caries occurs, the extractions are technically more challenging due to radiation complications such as trismus and post-RT extractions increase the risk of developing ORN [3]. It should be noted that a recent Cochrane review has not found any randomised controlled trials studying the extraction of teeth prior to RT[77].

Recently, some authors have claimed that such pre-RT extractions may actually increase the risk of developing ORN [4]. Newer RT technologies and techniques, such as dynamic and static intensity modulated RT, deliver a lower dose to the jaws and critical structures such as the parotid glands without compromise to the tumour dose. Coupled with improved oral hygiene methods both ORN and the development of post-RT dental disease, is likely to result in an improved probability of retaining teeth [6, 78].

The aim of this study was to examine the impact of dental extractions on the development of ORN.

## Materials and Methods

### *Participant selection*

Patients over the age of 18 with oropharyngeal cancer treated with curative intent definitive and/or postoperative RT at two tertiary hospitals in an Australian state capital from 2005-2011 were invited to participate in the study. Patients underwent treatment planning through a multidisciplinary head and neck clinic and all received dental assessment, primary dental treatment and oral hygiene instruction before being discharged back to community dental clinics. Oropharyngeal cancer was chosen specifically as the standard treatment is chemoradiation, providing radiation delivery to the jaws. The dates chosen allowed sufficient post-treatment time to capture late complications, specifically ORN. Institutional ethics approval was obtained and participants provided written informed consent. 190 participants completed the study, and 47 declined to participate. Data was collected between July and December 2014.

### *Data collection*

Consenting participants had their demographic and treatment data retrieved from hospital databases. Age, gender and smoking status were recorded. Diagnostic data included tumour location, tissue diagnosis, p16 status and TNM classification. Treatment data included radiation dose and site as well as the use and synchronicity of chemotherapy. Participants were given questionnaires requesting further information regarding their dental health and treatment in the preceding months before, during and following RT. Specifically, the location, timing and number of dental extractions were recorded. Subjective dental hygiene was recorded for pre- and post-treatment and participants were asked to disclose dental habits, denture use and service utilisation. The questionnaire gathered information regarding exposed bone after radiation treatment including duration,

quadrant location and treatment with either surgical intervention and/or hyperbaric oxygen. Location site was confirmed with medical records and radiographs.

All data was de-identified, tabulated and stored in a secure database.
A diagnosis of ORN was recorded where an area of exposed bone was present in radiation fields for at least 3 months, and/or required treatment with surgical intervention or hyperbaric oxygen therapy without evidence of tumour recurrence.
Data underwent statistical analysis provided by an independent external statistician using Stata statistical software v12.0 (Statacorp, College Station, TX, USA).

**Results**

190 participants met the criteria and were included in the study, of which 132 (69.5%) were from hospital 1, and 58 (30.5%) were from hospital 2. 157 (82.6) were males and 33 (17.3%) were females. The mean age was 64.9 (34.1-89.0, SD 8.3) with mean female age 61.2 and mean male age 65.7. (Table 2.1).

| **Tumour Site** | **Cases** | **T Stage** | **Cases** | **Prog Stage** | **Cases** |
|---|---|---|---|---|---|
| Tonsil | 102 | TX | 2 | Stage I | 5 |
| Base of Tongue | 68 | T0 | 3 | Stage II | 8 |
| Soft Palate | 3 | T1 | 44 | Stage III | 31 |
| Oropharynx Other or Unspecified | 17 | T2 | 66 | Stage IVA | 134 |
| **P16 status** | **Cases** | T3 | 43 | Stage IVB | 7 |
| Positive | 102 | T4a | 27 | Not recorded | 5 |
| Negative | 15 | T4b | 1 | | |
| Unknown | 73 | T Not recorded | 4 | | |
| **Smoking status** | **Count** | **N Stage** | | | |

| | | | | | |
|---|---|---|---|---|---|
| Current smoker | 24 | N0 | 22 | | |
| Ex-smoker | 78 | N1 | 32 | | |
| Non-smoker | 40 | N2a | 19 | | |
| Unknown | 48 | N2b | 74 | | |
| **Morphology** | **Count** | **N2c** | **24** | | |
| Squamous cell carcinoma | 181 | N3 | 6 | | |
| Other | 9 | N Not recorded | 4 | | |

*Table 2.1 Participant demographics*

*Treatment Modality*

All participants underwent curative intent RT as required by the study protocol. 167 (87.9%) underwent concurrent chemotherapy and RT. 21 (11.1%) underwent RT alone, and 2 (1.1%) underwent sequential chemotherapy and RT. The mean RT dose administered was 68 Gray (30-77, SD 5.9).

*Pre-Radiotherapy Dental Extractions*

4 participants (2.1%) were edentulous prior to treatment. 129 (67.9%) of participants underwent dental extractions as part of their pre-RT treatment. 13 of this group underwent full clearances. It is important to note that of 129 cases who had pre-RT extractions, 20 (15.5%) went on to have post-RT extractions, leaving 109 having only pre-RT extractions. The mean number of teeth extracted for all cases was 5.1 (Range 0-24, SD 5.4). Teeth were extracted prior to RT at a total of 364 quadrant-extractions. More extractions were performed in the mandible at a ratio of 1.7:1. Quadrants 1 to 4 had 77, 72, 102 and 113 quadrant-extractions respectively. Current smokers were more likely to have pre-RT extractions (p=0.02). (Table 2).

| **Pre- and Post-Radiotherapy Dental Extractions** | **Count** | **% of Total** |
|---|---|---|
| Pre-RT (total) | 129 | 67.9% |

| | | |
|---|---|---|
| Pre-RT (only) | 109 | 57.4% |
| Pre-RT Full Clearance | 13 | 6.8% |
| During RT | 0 | 0% |
| Post-RT (total) | 30 | 15.8% |
| Post-RT (only) | 10 | 5.3% |
| Pre- and Post-RT | 20 | 10.5% |
| Pre- and/or Post-RT | 139 | 73.2% |
| No extractions (Dentate) | 47 | 24.7% |
| Edentulous prior to treatment | 4 | 2.1% |

*Table 2.2 Dental extractions*

*Extractions during radiotherapy*

No participants had dental extractions during RT.

*Post-Radiotherapy Dental Extractions*

30 participants underwent post-RT extractions, with 10 cases having them alone. The mean number of teeth extracted after RT for all cases was 0.85 (Range 0-20, SD 3.0). Teeth extracted post-RT were balanced across the mouth, with extractions from quadrant 1 to quadrant 4 as 16, 15, 15 and 16 respectively.

*Osteoradionecrosis*

29 participants (15.3%) had developed ORN at the time of the study. ORN developed in the mandible for 26 participants, and maxilla for 3 participants.

25 of the 29 cases of ORN (86.2%) occurred in participants who underwent pre-RT extractions, and 22 of the 29 cases of ORN (75.9%) were in sites of pre-RT extraction. Of the 25, 2 cases of ORN developed in participants who had full clearances, and 5 developed in participants who had both pre- and post-RT extractions.

4 cases of ORN (13.8%) developed in the site of post-RT extraction, and 3 (10.3%) were in the same quadrant that had undergone both pre- and post-RT extractions. 2 dentate participants developed ORN without undergoing pre- or post-RT extractions. No participants who were edentulous at the beginning of treatment developed ORN.

*Oral Hygiene Status*

Oral hygiene status was self reported, with an overall status, brushing times per day and dental visits per year recorded. Participants gave scores for their hygiene both pre- and post-RT, reported as poor, fair, good or excellent. Post-treatment the results polarised and the excellent and poor groups made net gains (Table 3).

| **Oral Hygiene** | **Poor** | **Fair** | **Good** | **Excellent** |
|---|---|---|---|---|
| Pre-RT | 2.6% | 19.6% | 57.7% | 20.1% |
| Post-RT | 5.8% | 11.6% | 42.9% | 39.7% |
| Net change | +3.2% | -7.9% | -14.8% | +19.6% |

*Table 2.3 Oral Hygiene*

*Dental Extractions*

Linear regression testing different subgroups of extractions as variables and development of ORN as the outcome yielded a number of significant results. Pre-RT dental extractions regardless of post-RT extractions, in isolation, combined with post-RT extractions in toto or using an and/or approach resulted in an increased odds of developing ORN at the 95% level, specifically 3.19, 5.19, 7.50 and 5.42 respectively.

No extractions were performed during RT.

Post-RT extractions were analysed using the same method, however in the categories described yielded significant results only when grouped with pre-RT extractions. It is important to note however, that the sign was positive despite lack of significance.

The numbers of extractions were tested either as a continuous quantitative variable per extraction and as a series of quantitative groups, specifically zero, one to zero and greater than eight, using zero as the control. Participants had 0 to 24 teeth extracted pre-RT. The odds were 1.13 per extraction and were significant at the 95% level. In the discrete groups there was significance for extractions greater than eight, with odds of 5.28, compared no zero extractions. For post RT extractions, with a range of 0-20, the same significance was not demonstrated in the post-RT group for either number as quantitative, or discrete as zero, one or greater than one, despite again having a positive odds. (Table 4).

| Extraction | OR | p | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|
| Pre, regardless of post | 3.19 | 0.040 | 1.05 | 9.62 |
| Post, regardless of pre | 1.87 | 0.21 | 0.71 | 4.93 |
| Post, not pre | 5.62 | 0.11 | 0.69 | 45.90 |
| Pre, not post | 5.19 | 0.032 | 1.15 | 23.42 |
| Pre and post | 7.50 | 0.023 | 1.32 | 42.77 |
| Pre and/or post, 'any extraction' | 5.42 | 0.025 | 1.24 | 23.76 |
| Pre, number (quant, cont), per exo | 1.13 | 0.001 | 1.05 | 1.21 |
| Pre, 1-7 (qual) | 1.66 | 0.44 | 0.46 | 5.98 |
| Pre, >8 (qual) | 5.28 | 0.005 | 1.67 | 16.73 |
| Post, number (quant, cont), per exo | 1.06 | 0.27 | 0.95 | 1.18 |
| Post, >1 (qual) | 1.85 | 0.21 | 0.71 | 4.84 |

*Table 2.4 Dental extractions and osteoradionecrosis*

Pearson chi-squared test was used to determine if the development of ORN was related to pre-RT extractions in the same quadrant, reporting chi2(1) 11.02 (Pr=0.001), indicating a significant association.

Additional variables were tested to assess their effect on development of ORN, with significant increased odds returning for current smoking status between current smokers (C), and ex-smokers (E) and non-smokers (N), (OR 3.6, p=0.028) and p16 status negative (OR 9.04, p<0.001). Site and morphology did not return any significant results. (Table 5).

| Variable | OR | p | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|
| Smoking, C v E | 3.60 | 0.028 | 1.15 | 11.32 |
| Smoking, C v N | 2.88 | 0.11 | 0.80 | 10.43 |

| | | | | |
|---|---|---|---|---|
| P16, -ve | 9.04 | <0.001 | 2.66 | 30.73 |
| Gender, male | 1.98 | 0.29 | 0.056 | 6.99 |
| Age, per year | 1.012 | 0.59 | 0.097 | 1.06 |
| Hospital | 1.03 | 0.91 | 0.44 | 2.42 |

*Table 2.5 Demographics and osteoradionecrosis*

Multiple logistic regression was then performed using age, p16 and smoking status, and pre and post-RT extractions. Significant results were returned for p16 status (coeff 0.093, p=0.049) and pre-RT extractions (coeff 0.13, p=0.025). Post-RT extractions effect size was comparable but not significant (coeff 0.098, p=0.18).

*Participants who declined to be involved*

Limited data was available for those who declined to be involved in the study. From what data was available, the demographics of this group were similar to that of the study population. The mean age was 61 compared to 64.9 of the study group, slightly fewer males (76% compared with 82%), similar site of disease (majority tonsil followed by base of tongue), radiotherapy dose 65 compared with 68Gy. Disease severity showed a similar distribution, however there was a trend towards higher T1 in the declined group (36% compared with 23%) and lower T4a in the declined group (9% compared with 14%). Nodal disease was matched for both groups.

**Discussion**

In this study, pre-RT dental extractions were shown to significantly increase the odds of developing ORN, regardless of whether the extractions were exclusive or inclusive of post-RT extractions. The odds of developing ORN were increased in comparable amounts when post-RT extractions were tested against no extractions, however this was found to be statistically insignificant.

However, there were a far greater number of participants receiving pre-RT extractions (129 cases) compared with those receiving post-RT extractions (30 cases). As a tooth can only be extracted once, it is not unreasonable to suggest that you can reduce pre-RT extractions by delaying these for 6 weeks or so and thus produce a greater number of post-RT extractions. The same logic would follow that this would present the same or increased risk of ORN, however now attributing it to the post-RT extractions. This is, however, the exact reasoning but with the reverse effect that has resulted in such a large

number of pre-RT extractions being undertaken, and has been shown in this study to not reduce the risk of ORN. The alternate hypothesis is that it is not either pre-RT extractions or post-RT extractions that is the culprit, but extractions in general are, regardless of timing. This could be extended to oral health, as the root cause of extractions through caries or periodontal disease, is the cause of the increased risk of developing ORN, as some researchers have found. It should be highlighted that patients with poor oral health are more likely to undergo dental extractions, thus placing them at higher risk of developing ORN [79, 80].

If pre-RT extractions are taken on an intention to treat, ie regardless of post-RT extraction status, the odds ratio of developing ORN are 3.19 (p=0.040). Decanting this by removing post-RT extractions increases the odds ratio to 5.19 (0.032). It is interesting that these odds are similar to post-RT extractions (excluding pre-RT extractions) with odds of 5.62 (p=0.11). What is more interesting is that these pre-RT extractions do not appear to protect against post-RT extractions, as two thirds of the post-RT extraction group had pre-RT extractions as well. The other third (n=10), represent only 16.4% of the group who had no pre-RT extractions. If ‘any extraction’ is used as the variable, the odds ratio remains similar to that of either pre- or post-RT extractions, however is now significant (OR 5.42, p=0.025).

It would make sense that if ‘any extraction’ increases the risk of developing ORN then an increased number of extractions would increase the odds of developing ORN, and this is exactly what was found. When pre-RT dental extractions increase, the odds of developing ORN increase by 1.13 per tooth extracted (p=0.001). For post-RT extractions the odds increased at a smaller, insignificant rate (1.06, p=0.27). For those that had both pre- and post-RT extractions, the odds of developing ORN were incredibly high (7.50, p=0.023), which is related to increased extraction number, extraction incidences and, likely, an underlying oral health issue.

The hypothesis that any extraction increases the risk of ORN, raises a number of questions. Firstly, should sound teeth in radiation fields be extracted prior to RT? Secondly, can compromised or ‘borderline’ teeth be left or restored prior to RT and have a reasonable prognosis? And thirdly, if teeth are hopeless and must be extracted, when should this be performed? While this study did not look at the extraction indications, the findings can shed light on these questions.

Extraction of sound teeth, ie those that would not be extracted in participants not planned for RT should not be performed in those who are planned for RT, as these extractions increase the risk of developing ORN, and may reduce the post-treatment quality of life.

Extraction of compromised teeth, ie those that would generally not be extracted in participants not planned for RT but would require some degree of restoration, requires good clinical judgement. The oral cavity will undergoing significant stress in the post-irradiation period, however the dentition can be maintained[6]. Guidelines for management of the irradiated patient have been published by the authors in the past [81]. It should be noted as an alternative to extraction, endodontic treatment is successful in the irradiated patient[51, 82, 83] and to date is not associated with ORN.

Extraction of hopeless teeth, ie those that would be extracted regardless of RT planning, does not warrant an argument against performing the extractions, but rather the timing of such extractions. If performed prior to RT, the rapid turnover of bone in the healing socket is exposed to RT – the oncologic management cannot be delayed until the socket has achieved full bony resolution. If performed afterwards, the extraction is now performed in conditions of compromised healing. Both instances are less than ideal, and there is no current evidence to determine when is the best time for extraction.

**Further Research**

High quality evidence requires high quality data, although it is not possible to blind participants or researchers against extraction and not ethical to assign someone to randomly having their teeth extracted. A prospective study with meticulous data collection would be the only feasible solution. If the teeth were required to be extracted, a useful study would be on the timing of such extractions- should they occur in the pre-RT period when time prior to treatment is limited, or can they be delayed until the immediate post-RT period?

**Limitations**

It is prudent to address the limitations of a study before discussing the merits of the results so as to ensure the outcomes are viewed in the correct light, and, more importantly, that future studies may be planned accordingly to account for such limitations and produce higher quality data.

In this study, there are number of limitations. There is no true control, nor is there a pre-treatment quality of life baseline, and there is evidence to suggest that longer term quality of life relates to baseline[84, 85]. Due to the nature of the study design, there are opportunities for bias to occur with participants selecting into and out of the study due to personal reasons, for example, developing ORN and desiring to express their concerns. Additionally there is survivorship bias, as all participants have been able to complete the requirements of the study, which selects for p16 positive malignancies and the inherent prognostic factors [9, 86].

It would have been ideal for the participants to have had each tooth individually assessed by the same clinician in the pre-RT period, and record details such as extraction indication, extraction procedure use of adjuvants and time to RT, as well as provide comparison with the same patients at follow up, but this was not possible due to the study design.

**Conclusion**

Pre-RT dental extractions do not appear to protect against ORN. With improved prevention methods and dose limiting technology the chances of long-term tooth retention are greatly improved.

## Chapter 3:

## Pre-radiotherapy dental extractions and health-related quality of life

*Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology (2016) Under Submission*

### Introduction

Radiotherapy (RT) is widely utilised for the management of head and neck cancer (HNC) and is associated with significant morbidity, manifest during treatment and often persisting permanently. One of the most feared late sequelae is osteoradionecrosis of the jaws (ORN), a condition of impaired wound healing characterised by non-vital bone in radiation fields not related to tumour recurrence[1]. Many risk factors for ORN exist including radiation dose, field and fractionation, tumour location, smoking and alcohol use, general health and nutrition status, oral health and oral hygiene. There also exist triggers that increase the likelihood of ORN developing, such as dental extractions, dental implants, surgery or poor fitting prostheses [2] as well as any residual foci of infection[76].

To minimise the risk of ORN and other radiation-related negative effects on the oral cavity, it is recommended that all patients are seen by a dental clinician prior to the commencement of treatment. At this visit, the oral status is assessed and appropriate dental treatments are completed. The dental needs of patients diagnosed with HNC are often quite high, and patients frequently present with periodontal disease and caries [13].

An important factor when understanding treatment effects of neoplastic disease is the patient's quality of life. A cancer diagnosis is often traumatic, and the treatment received has significant morbidity. In the case of head and neck cancer treated with RT, there can be significant effects on aesthetics, speech, eating and pain, as well as general effects on emotional state, social state and a general functional level [7]. There are numerous quality of life instruments available for the clinician or researcher to use, with a recent review finding 57 separate head and neck specific instruments published [87]. Quality of life instruments attempt to measure the human experience in order to produce a meaningful, thorough and comparable quantity that can be used to ascertain treatment effectiveness beyond the purely biological. This is obviously not an easy task.

It is logical on face value and has been reflected in the literature that fewer teeth are associated with reduced quality of life [10]. There are no studies published to date on the impact of RT related dental extractions on quality of life. As teeth are often extracted in the pre-RT period, it is hypothesised that dental extractions in this population result in a reduced oral health related quality of life. The competing theory is that pre-RT dental extractions provide a protective effect against outcomes that stand to impair quality of life, such as ORN, in such a significant way as to overpower the quality of life effect of tooth loss and provide a net benefit. In this study we aim to understand the effect that dental extractions had on quality of life for patients receiving RT for oropharyngeal cancer (OPC).

## Materials and Methods

*Participant selection*

Patients over the age of 18 with OPC treated with curative intent definitive and/ or postoperative RT at two tertiary hospitals in an Australian state capital from 2005-2011 were invited to participate in the study. Patients underwent treatment planning through a multidisciplinary head and neck clinic and all received dental assessment, primary dental treatment and oral hygiene instruction before being discharged back to community dental clinics The dates chosen allowed sufficient post-treatment time to capture late complications, specifically ORN with a minimum time of 3 years. Participants were required to be consenting and free to withdraw at any stage as per ethics approval. 190 participants completed the study, and 47 declined to participate. Data was collected between July and December 2014.

*Data collection*

Consenting participants had their demographic and treatment data retrieved from hospital databases. Age, gender and smoking status were recorded. Diagnostic data included tumour location, tissue diagnosis, TNM staging and p16 status. Treatment data included radiation dose and site as well as the use and synchronicity of chemotherapy.
Participants were given questionnaires requesting further information regarding their dental health and treatment in the preceding months before, during and following RT. Specifically, the location, timing and number of dental extractions were recorded. Subjective dental hygiene was recorded for pre- and post-treatment and participants were asked to disclose dental habits, denture use and service utilisation. The questionnaire gathered information regarding exposed bone after radiation treatment including duration,

quadrant location and treatment with either surgical intervention and/or hyperbaric oxygen. Location site was confirmed with medical records and radiographs.

Participants were given two self-reported quality of life instruments, the Oral Health Impact Profile 14 (OHIP-14)[88], and the Functional Assessment of Cancer Therapy – Head and Neck (FACT Head and Neck)[89] which they completed and returned. As this is a retrospective study, there was no opportunity to collect a baseline quality of life assessment.

All data was de-identified, tabulated and stored in a secure database.

The quality of life instruments were administered according to their guidelines.

OHIP-14 scores were individually calculated based on additive measures.

FACT Head and Neck scores were individually calculated according to the weighted method. Subset scores were recorded according to the Functional Assessment of Chronic Illness Therapy (FACIT) guidelines and recorded as physical well-being, social well-being, emotional well-being, functional well-being and head and neck specific. Derived scores were also calculated according to the guidelines and recorded as FACT-G, FACT-HN Total and Fact-HN Trial Outcome Index. FACT-G scores represent a general endpoint utilising the subsets of Physical, Social, Emotion and Functional Well Being are comparable with other FACIT family scores. FACT- Trial Outcome Index represents a physical and functional endpoint, which is calculated from Physical and Functional Well Being, and the Head and Neck specific score. The FACT total score encompasses all the subsets.

Data underwent statistical analysis provided by an independent external statistician using Stata statistical software v12.0 (Statacorp, College Station, TX, USA).

**Results**

190 participants met the criteria and were included in the study, of which 132 (69.5%) were from hospital 1, and 58 (30.5%) were from hospital 2.  157 (82.6) were males and 33 (17.3%) were females. The mean age was 64.9 (34.1-89.0, SD 8.3) with mean female age 61.2 and mean male age 65.7.

Approximately half of the cases were tonsillar primary tumours (53.7%) followed by base of tongue (35.8%). Of known p16 status cases the great majority were positive (87.2%). Smoking status was divided into current smokers, ex-smokers and lifelong non-smokers,

and respectively represented 16.9%, 54.9% and 28.2%, indicating over three-quarters were current or ex-smokers. The majority of histopathological diagnoses were SCC (95.3%) (Table 1).

*Table 3.1 Participant Demographics*

| **Tumour Site** | **Cases** | **T Stage** | **Cases** | **Prog Stage** | **Cases** |
|---|---|---|---|---|---|
| Tonsil | 102 | TX | 2 | Stage I | 5 |
| Base of Tongue | 68 | T0 | 3 | Stage II | 8 |
| Soft Palate | 3 | T1 | 44 | Stage III | 31 |
| Oropharynx Other or Unspecified | 17 | T2 | 66 | Stage IVA | 134 |
| **P16 status** | **Cases** | T3 | 43 | Stage IVB | 7 |
| Positive | 102 | T4a | 27 | Not recorded | 5 |
| Negative | 15 | T4b | 1 | | |
| Unknown | 73 | T Not recorded | 4 | | |
| **Smoking status** | **Count** | **N Stage** | | | |
| Current smoker | 24 | N0 | 22 | | |
| Ex-smoker | 78 | N1 | 32 | | |
| Non-smoker | 40 | N2a | 19 | | |
| Unknown | 48 | N2b | 74 | | |
| **Morphology** | **Count** | **N2c** | **24** | | |
| Squamous cell carcinoma | 181 | N3 | 6 | | |
| Other | 9 | N Not recorded | 4 | | |

*Treatment Modality*

All participants underwent RT as required by the study protocol. 167 (87.9%) underwent concurrent chemotherapy and RT. 21 (11.1%) underwent RT alone, and 2 (1.1%) underwent sequential chemotherapy and RT. The mean RT dose administered was 68 Gray (30-77, SD 5.9).

*Pre-Radiotherapy Dental Extractions*

4 participants (2.1%) were edentulous prior to treatment. 129 (67.9%) of participants underwent dental extractions as part of their pre-RT treatment. 13 of this group underwent full clearances. Of the 129 cases who had pre-RT extractions, 20 (15.5%) went on to have post-RT extractions, leaving 109 having only pre-RT extractions. The mean number of teeth extracted for all cases was 5.1 (Range 0-24, SD 5.4). Teeth were extracted prior to RT at a total of 364 quadrant-extractions. More extractions were performed in the mandible at a ratio of 1:1.7. Quadrants 1 to 4 had 77, 72, 102 and 113 quadrant-extractions respectively.

*Extractions during radiotherapy*

No participants had dental extractions during RT treatment.

*Post-Radiotherapy Dental Extractions*

30 participants underwent post-radiotherapy extractions, with 10 cases having them alone. The mean number of teeth extracted after RT for all cases was 0.85 (Range 0-20, SD 3.0). Teeth extracted post RT were balanced across the mouth, with extractions from quadrant 1 to quadrant 4 as 16, 15, 15 and 16 respectively (Table 2).

*Table 3.2 Dental extractions*

| **Extractions** | **Count** |
|---|---|
| Pre-RT extractions | 129 |
| Pre-RT full clearance | 13 |
| Pre-RT extractions only | 109 |
| Edentulous prior to treatment | 4 |

| | |
|---|---|
| Post RT extractions | 30 |
| Post RT extractions only | 10 |
| Pre- and Post-RT | 20 |
| Pre- and/or Post-RT | 139 |
| No extractions (Dentate) | 47 |

*Osteoradionecrosis*

29 participants (15.3%) had developed ORN at the time of the study. ORN was 5.8 times more common in the mandible than the maxilla.

25 of the 29 cases of ORN (86.2%) occurred in participants who underwent pre-RT extractions, and 22 of the 29 cases of ORN (75.9%) were in sites of pre-RT extraction. Of the 25, 2 cases of ORN developed in participants who had full clearances, and 5 developed in participants who had both pre- and post-RT extractions.

4 cases of ORN (13.8%) developed in the site of post-RT extraction, and 3 (10.3%) were in the same quadrant that had undergone both pre- and post-RT extractions. 2 dentate participants developed ORN without undergoing pre- or post-RT extractions. No participants who were edentulous at the beginning of treatment developed ORN.

*Oral Hygiene Status*

Oral hygiene status was self reported, with an overall status, brushing times per day and dental visits per year recorded. Participants gave scores for their hygiene both prior to treatment and at the time of questionnaire, reported as poor, fair, good or excellent. Post-treatment the results polarised and the excellent and poor groups made net gains (Table 3).

*Table 3.3 Oral Hygiene Status*

| **Oral Hygiene** | **Poor** | **Fair** | **Good** | **Excellent** |
|---|---|---|---|---|
| Pre-RT | 2.6% | 19.6% | 57.7% | 20.1% |
| Post-RT | 5.8% | 11.6% | 42.9% | 39.7% |
| Net change | +3.2% | -7.9% | -14.8% | +19.6% |

*Quality of Life Measures*

The range of values representing quality of life was broad, with the OHIP-14 scores ranging from the lowest possible score to 3 points below the highest possible score. A similar range was found for the FACT-Head and Neck subsets, with the results occupying a large proportion of the available options.

It must be noted that the values for the OHIP-14 and the FACT-H&N measures have different meanings of their sign, ie a higher score for the OHIP-14 represents a poorer quality of life, whereas a higher score for the FACT-Head and Neck represents a richer quality of life. To derive the OHIP-14 mean as a percentage of the theoretical maximum, the inverse was used as to be more comparable (Table 4).

*Table 3.4 Quality of life outcomes*

| **Instrument** | **Mean** | **Min (Actual)** | **Max (Actual)** | **St Dev** |
|---|---|---|---|---|
| OHIP 14 | 16.1 | 0 | 53 | 12.7 |
| PWB | 23.5 | 3 | 28 | 4.7 |
| SWB | 21.6 | 0 | 28 | 6.6 |
| EWB | 20.0 | 5 | 24 | 4.3 |
| FWB | 22.0 | 4 | 28 | 5.7 |
| HNCS | 27.1 | 8 | 40 | 7.6 |
| FACT TOI | 72.6 | 19 | 96 | 15.7 |
| FACT G | 87.1 | 36 | 108 | 17.1 |
| FACT H&N | 114.2 | 44 | 147 | 22.9 |

*OHIP-14*

From the OHIP-14 data, is can be seen that female gender was associated with a significantly worse quality of life (6.8 points). Other outcomes that negatively affected the quality of life according to the OHIP-14 score at the 5% level were p16 status and smoking status. p16 negative cases had poorer quality of life, as did current and ex-smokers, with current smokers faring worse.

Pre-RT dental extractions by number revealed that >8 were associated with a significantly worse quality of life than those who had no extractions. While 1-7 pre-RT extractions and post-RT extractions were associated with a reduced quality of life, this was not found to be significant at levels applied. When pre-RT dental extractions were taken as a binary yes or no, the effect on the quality of life was negative but not statistically significant.

Other measures associated with a significantly reduced quality of life included pre-RT full clearance (14.05, p=0.046), and development of ORN (4.74, p=0.036). Current excellent dental hygiene was associated with a slightly improved quality of life (-1.92 points, p=0.004).

There was not a great range of RT doses received to determine a significant effect on quality of life. When the doses are separated into the groups ‘less than 70 Gray’ and ‘greater than or equal to 70 Gray’ there is a negative but not significant effect on quality of life (3.38, p=0.54). Treatment received i.e. synchronised chemoradiotherapy and other intervention groups did not produce significant results, but again there was a great degree of homogeneity in the data (Table 5).

*Table 3.5 Linear regression for OHIP-14*

| **OHIP-14** | | | | |
|---|---|---|---|---|
| **Variable** | **Coefficient** | **P value** | **95% Confidence Interval** | |
| Age | -0.15 | 0.119 | -0.33 | 0.04 |
| Gender (M) | -6.84 | 0.005* | -11.53 | -2.14 |
| Morphology | -3.33 | 0.44 | -11.87 | 5.22 |
| p16 (+ve) | -8.21 | 0.025* | -15.38 | -1.03 |
| Smoking Ex vs C | -6.14 | 0.039* | -11.96 | -0.31 |
| Smoking N vs C | -6.24 | 0.058* | -12.69 | 0.20 |
| Pre RT exo 1-7 vs 0 | 3.82 | 0.090 | -0.59 | 8.23 |
| Pre RT exo >8 vs 0 | 4.82 | 0.033* | 0.40 | 9.23 |

| | | | | |
|---|---|---|---|---|
| Post-RT exo | 3.56 | 0.16 | -1.40 | 8.52 |

*FACT Head and Neck Subset Scores*

The FACT- Head and Neck subset scores were analysed to further understand if associations could be made between particular domains of quality of life and interventions received. Here it can be seen that there is a significant association across all domains between reduced quality of life and smoking status as either current and or ex compared with lifelong nonsmokers. p16 negative cases are associated with reduced quality of life in the Social and HNCS domains. Female gender was significantly associated with reduced quality of life in the Emotional Well Being domain (Table 6, Table 7).

*Table 3.6 Linear regression for FACT Head and Neck*

| **Physical Well Being** | | | | |
|---|---|---|---|---|
| **Variable** | **Coefficient** | **P value** | **95% Confidence Interval** | |
| Age | 0.031 | 0.38 | -0.038 | 0.099 |
| Gender (M) | 0.78 | 0.38 | -0.98 | 2.55 |
| Morphology | 1.31 | 0.41 | -1.84 | 4.47 |
| p16 (+ve) | .66 | 0.64 | -2.15 | 3.47 |
| Smoking Ex vs C | 2.27 | 0.037* | 0.14 | 4.40 |
| Smoking N vs C | 2.78 | 0.021* | 0.42 | 5.13 |
| Pre RT exo 1-7 vs 0 | -0.52 | 0.53 | -2.17 | 1.12 |
| Pre RT exo >8 vs 0 | -0.07 | 0.93 | -1.72 | 1.58 |
| Post-RT exo | -0.27 | 0.77 | -2.11 | 1.57 |
| **Social Well Being** | | | | |
| **Variable** | **Coefficient** | **P value** | **95% Confidence Interval** | |
| Age | -0.01 | 0.80 | -0.11 | 0.09 |
| Gender (M) | 0.65 | 0.51 | -1.87 | 3.16 |
| Morphology | 1.50 | 0.66 | -2.98 | 5.98 |

| | | | | |
|---|---|---|---|---|
| p16 (+ve) | 3.80 | 0.047* | 0.06 | 7.55 |
| Smoking Ex vs C | 2.87 | 0.06 | -0.12 | 5.86 |
| Smoking N vs C | 5.23 | 0.002* | 1.93 | 8.54 |
| Pre RT exo 1-7 vs 0 | -1.66 | 0.16 | -4.00 | 0.67 |
| Pre RT exo >8 vs 0 | -0.71 | 0.55 | -3.05 | 1.62 |
| Post RT exo | -0.26 | 0.84 | -2.87 | 2.35 |
| **Emotional Well Being** | | | | |
| **Variable** | **Coefficient** | **P value** | **95% Confidence Interval** | |
| Age | 0.04 | 0.17 | -0.19 | 0.10 |
| Gender (M) | 2.06 | 0.01* | 0.47 | 3.66 |
| Morphology | 1.33 | 0.36 | -1.55 | 4.22 |
| p16 (+ve) | 1.07 | 0.40 | -1.44 | 3.58 |
| Smoking Ex vs C | 0.97 | 0.33 | -1.01 | 2.95 |
| Smoking N vs C | 2.53 | 0.02* | 0.34 | 4.73 |
| Pre RT exo 1-7 vs 0 | -0.75 | 0.92 | -1.59 | 1.43 |
| Pre RT exo >8 vs 0 | 0.21 | 0.79 | -1.31 | 1.71 |
| Post RT exo | 0.14 | 0.87 | 1.54 | 1.83 |
| **Functional Well Being** | | | | |
| **Variable** | **Coefficient** | **P value** | **95% Confidence Interval** | |
| Age | 0.03 | 0.54 | -0.06 | 0.11 |
| Gender (M) | 0.52 | 0.63 | -1.63 | 2.70 |
| Morphology | 1.57 | 0.42 | -2.27 | 5.41 |
| p16 (+ve) | 3.15 | 0.064 | -0.19 | 6.48 |
| Smoking Ex | 3.75 | 0.005* | 1.13 | 6.36 |

| | | | | |
|---|---|---|---|---|
| vs C | | | | |
| Smoking N vs C | 5.13 | 0.001* | 2.24 | 8.03 |
| Pre RT exo 1-7 vs 0 | -1.09 | 0.29 | -3.10 | 0.92 |
| Pre RT exo >8 vs 0 | -0.22 | 0.83 | -2.22 | 1.79 |
| Post RT exo | -1.16 | 0.31 | -3.40 | 1.07 |
| **HNCS** | | | | |
| **Variable** | **Coefficient** | **P value** | **95% Confidence Interval** | |
| Age | 0.03 | 0.65 | -0.09 | 0.14 |
| Gender (M) | 0.76 | 0.60 | -2.11 | 3.63 |
| Morphology | 1.43 | 0.58 | -3.70 | 6.55 |
| p16 (+ve) | 4.55 | 0.035* | 0.33 | 8.77 |
| Smoking Ex vs C | 4.17 | 0.017* | 0.75 | 7.60 |
| Smoking N vs C | 3.66 | 0.058 | -0.13 | 7.44 |
| Pre RT exo 1-7 vs 0 | -2.26 | 0.096 | -4.93 | 0.40 |
| Pre RT exo >8 vs 0 | -1.150 | 0.28 | -4.13 | 1.20 |
| Post RT exo | -1.68 | 0.27 | -4.66 | 1.30 |

*Table 3.7 Fact Head and Neck Derived Scores*

| **FACT TOI** | | | | |
|---|---|---|---|---|
| **Variable** | **Coefficient** | **P value** | **95% Confidence Interval** | |
| Age | 0.08 | 0.48 | -0.15 | 0.31 |
| Gender (M) | 2.07 | 0.49 | -3.85 | 7.98 |
| Morphology | 4.31 | 0.42 | -6.23 | 14.86 |
| p16 (+ve) | 8.36 | 0.069 | 0.66 | 17.38 |

| | | | | |
|---|---|---|---|---|
| Smoking Ex vs C | 10.19 | 0.005* | 3.11 | 17.26 |
| Smoking N vs C | 11.57 | 0.004* | 3.74 | 19.39 |
| Pre RT exo 1-7 vs 0 | -3.87 | 0.17 | -9.37 | 1.62 |
| Pre RT exo >8 vs 0 | -1.75 | 0.53 | -7.24 | 3.75 |
| Post RT exo | -3.12 | 0.32 | -9.25 | 3.02 |
| **FACT G** | | | | |
| **Variable** | **Coefficient** | **P value** | **95% Confidence Interval** | |
| Age | 0.09 | 0.49 | -0.16 | 0.33 |
| Gender (M) | 4.01 | 0.22 | -2.43 | 10.46 |
| Morphology | 5.72 | 0.33 | -5.79 | 17.23 |
| p16 (+ve) | 8.68 | 0.09* | -1.40 | 18.74 |
| Smoking Ex vs C | 9.86 | 0.014* | 2.06 | 17.66 |
| Smoking N vs C | 15.68 | <0.0001* | 7.05 | 24.31 |
| Pre RT exo 1-7 vs 0 | -3.35 | 0.27 | -9.36 | 2.67 |
| Pre RT exo >8 vs 0 | -0.80 | 0.80 | -6.81 | 5.22 |
| Post RT exo | -1.55 | 0.65 | -8.27 | 5.17 |
| **FACT TOTAL** | | | | |
| **Variable** | **Coefficient** | **P value** | **95% Confidence Interval** | |
| Age | 0.11 | 0.51 | -0.22 | 0.45 |
| Gender (M) | 4.78 | 0.28 | -3.87 | 13.42 |
| Morphology | 7.15 | 0.36 | -8.29 | 22.59 |
| p16 (+ve) | 13.23 | 0.051 | -0.09 | 26.54 |
| Smoking Ex vs C | 14.03 | 0.009* | 3.62 | 24.44 |

| | | | | |
|---|---|---|---|---|
| Smoking N vs C | 19.33 | 0.001* | 7.82 | 30.85 |
| Pre RT exo 1-7 vs 0 | -5.61 | 0.17 | -13.67 | 2.44 |
| Pre RT exo >8 vs 0 | -2.26 | 0.58 | -10.31 | 5.80 |
| Post RT exo | -3.23 | 0.48 | -12.23 | 5.77 |

**Discussion**

*Comparison of Quality of Life Instruments*

Murphy et al reports that Quality of Life instruments can be categorised as either site-specific (in this case, Head and Neck), symptom-specific or treatment-specific[85]. The selected instruments have been taken from different groups, namely the FACT- Head and Neck is a site-specific instrument, and the OHIP-14 is a symptom-specific instrument[87]. It was hypothesised that using instruments from differing paradigms would produce meaningful results. Additionally, data gained can introduce a comparison between the two instruments, as our literature review did not reveal any study comparing data from the OHIP-14 and the FACT- Head and Neck instruments. There was however, one study found which compared OHIP-14 to another member of the FACIT family, namely the FACT- Bone Marrow Transplant [90].

The studies have differing strengths and weaknesses. The OHIP-14 is derived from data collected from Australians and focuses on oral health symptoms [88]. This is important in order to capture any effect from oral hygiene as well as oral health interventions, such as dental extractions, as well as resulting in a high level of applicability as the current study population are Australian as well. The OHIP-14 is also short, and easy to use. However the OHIP-14 relates questions back to teeth, mouth or dentures, whereas the FACT-Head and Neck is more general, which may cause some answers to be different between the two. An example of this is the OHIP-14 question “Have you had painful aching in your mouth” and the FACT-Head and Neck statement “I have pain”. The FACT- Head and Neck instrument is utilised for breadth in that it captures general health data, and specificity in that the Head and Neck Specific questions have been determined especially for patients with head and neck cancer[89].

In this study, the mean of QoL outcomes is similar. The mean score expressed as a percentage of the theoretical maximum quality of life is 71.1% for OHIP-14 and 77% for FACT- Head and Neck. The OHIP-14 values ranged from the minimum theoretical (ie best possible quality of life) score of 0, to a maximum of 53 from the theoretical 56 (worst possible OHIP-14 score). Increased values for the two instruments have opposite meaning, and it can be seen that the FACT-Head and Neck ranges from a score of 147 of theoretical 148 (best possible score) and to a score of 44 from 0 (worst possible score). So while the means are comparable, it can be seen that the OHIP-14 reports a wider range, and the FACT-Head and Neck has a lesser range of negative quality of life scores.

*Demographics*

The participants were derived from two major and similar hospitals of within the same city, 69.5% from one and 30.5% from the other. The mean age was 64.9 (SD 8.3) and range 34.1 to 89, which is higher than that of diagnosis in HPV-associated (53 years) and non-HPV associated (57 years)[91], but when follow up time of 3 to 9 years is included then this number approaches that in the literature.

*Extractions*

A large number of participants (67.9%) underwent extractions (mean 5.1 teeth) as part of their pre-RT work-up. This is in keeping with the literature showing head and neck cancer patients present with high dental needs and unmanaged risk factors, poor oral health literacy and low engagement with the dental profession, often persisting post-treatment [13, 25, 92]. 15.5% (20) of those having pre-RT dental extractions went on to have post-RT dental extractions, with only 10 participants having post-RT extractions alone.

*Oral Hygiene*

Poor pre-RT dental hygiene habits have been published in the literature to persist following treatment [92], despite high adherence to oral hygiene methods leading to reduced complications [6, 93]. This must be seen as a joint responsibility of the patient and the head and neck oncology team, including the dental practitioner. In this study, we found that oral hygiene polarised following treatment, whereby the excellent and poor groups increased in number, and in fact the excellent group doubled from 20% to 39.7%. This was a subjective record, however it shows that despite morbid treatment there is chance of improving oral hygiene. All the participants in this study underwent dental consultation and

oral hygiene information prior to RT, and it is hypothesised that such oral health education and intervention can have a positive impact on hygiene practises.

*Quality of Life Outcomes*

This is the first study to the author's knowledge that investigates the effect of pre-radiotherapy dental extractions and quality of life. Some comparable data does exist for aspects of this study in the form of OHIP-14 and FACT H&N results but due to the large number of different instruments used by various institutions, opportunity for direct comparison is reduced.

The mean additive OHIP-14 score was 16.1, which is comparable to the score of 18.9 from a study of oral and oropharyngeal cancer survivors at least 6 months post-treatment, and contrasted to the mean of 5.9 from their control group[94]. Factors significantly reducing the quality of life per the OHIP-14 score were found to be female gender, p16 negative status, current vs never smoking status, current vs ex-smoking status, pre-RT dental extractions >8 and pre-RT full clearance. Development of ORN was associated with a worse quality of life. Excellent dental hygiene was found to improve quality of life.

In regards to the FACT- Head and Neck scores, similar results were found. Smoking status resulted in worse quality of life outcomes in the domains of physical, social, emotional and functional well-being. P16 negative status worsened social well-being, head and neck specific scores and FACT-G (general) scores. Female gender worsened quality of life in the emotional well-being domain.

Importantly, dental extractions both pre- and post-RT did not have a positive effect on quality of life post-treatment. While extractions did not have a significant relationship (beyond >8 extractions and OHIP-14 score), both groups were associated with negative effects on quality of life.

Smoking status has been found to be a predictor of not only post-treatment oral health related quality of life, but general health related quality of life in head and neck cancer survivors[8], and the current study confirms this relationship extends to a tiered system where current smokers, ex-smokers and non-smokers have improving quality of life. Additionally, our study confirms the previous findings that p16 positive cases have better

quality of life over their counterparts [95], often attributed to improved survival, younger age and lack of smoking, although other studies have found no difference [96].

It is interesting but not surprising that excellent dental hygiene was associated with an improved quality of life score. Improved oral hygiene should lead to improved oral function, and then translate into measurable quality of life differences.

*Clinical Implications*

The clinical implications are broad. Firstly, the dental needs of head and neck cancer patients are high, and clinicians should make the management of this a priority, as oral hygiene can improve, and is associated with the development of post-treatment complications. Secondly, dental extractions prior to RT do not improve post-treatment quality of life, and may worsen it. Such extractions therefore require great consideration. Thirdly, there are modifiable risk factors that can improve quality of life, namely smoking status, as well as non-modifiable risk factors such as female gender and HPV status that clinicians should identify as requiring greater support from a quality of life perspective.

*Further Research*

The domains covered by quality of life instruments in the head and neck population have a large amount of consistency. However, with more than 57 instruments to choose from, there is a great need that the advocates for various quality of life instruments in produce or choose a standard instrument, available freely and in multiple languages, so that the international community may benefit from improved communication of collected data and enable higher powered statistical comparison. A higher powered and prospective study investigating dental extractions and quality of life would add great weight to this discussion.

*Limitations*

It is prudent to address the limitations of a study before discussing the merits of the results so as to ensure the outcomes are viewed in the correct light, and, more importantly, that future studies may be planned accordingly to account for such limitations and produce higher quality data.

In this study, there are number of limitations. There is no true control, nor is there a pre-treatment quality of life baseline, and there is evidence to suggest that longer term quality of life relates to baseline[84, 85]. Due to the nature of the study design, there are opportunities for bias to occur with participants selecting into and out of the study due to personal reasons, for example, developing ORN and desiring to express their concerns. Additionally there is survivorship bias, as all participants have been able to complete the requirements of the study, which selects for p16 positive malignancies and the inherent prognostic factors [9, 86].

**Conclusion**

Pre-radiotherapy dental extractions may impact health-related quality of life.

# Chapter 4:
# Thesis Conclusion

## Dental Management of the Irradiated Patient

Dental management of the irradiated patient is firstly reduction of the disease burden and management of dental and periodontal disease prior to radiotherapy, followed by life-long intensive oral hygiene. The role of oral hygiene information (OHI) and education should not be diminished, as can be found in this study where all participants received comprehensive OHI and the group reporting excellent hygiene post-radiotherapy nearly doubled.

As radiotherapy delivery technology changes to deliver a lesser dose to major salivary glands and alveolar bone, so dental dogma must also be challenged. Teeth can be maintained following radiotherapy, and ORN can be dramatically minimised by both elimination of foci of infection and continuous intensive oral hygiene measures.

## Dental Extractions and Osteoradionecrosis

This study has shown that pre-radiotherapy dental extractions in increasing number are associated with a statistically significant increase in ORN, both as a yes/no and per extraction. Post-radiotherapy extractions were associated with an increased risk of ORN, however this was not statistically significant and there were a relatively small number of extractions. While it could be argued that denying pre-radiotherapy dental extractions is merely kicking the can down the road, it was also found that the majority of those who had post-radiotherapy dental extractions had pre-radiotherapy extractions as well. It is therefore important to divide these extractions into two groups; those that are prompted by significant disease burden, and those that are performed in the name of prophylaxis. Although this study is not powered enough to determine the extraction indication, it has been shown that any extraction confers a risk; in no situations were increased dental extractions associated with a reduction in the risk of ORN. Prophylactic dental extraction prior to radiotherapy should therefore, be questioned, as it may in fact be triggering the disease it is designed to reduce.

In regards to demographics, this study did not show an increased risk for age or gender in regards to ORN, however the treatment group was quite homogenous in this regard. It was shown that smokers who continue their habit following radiotherapy are at an increased

risk of developing ORN. No tumour subgroup was associated with a higher risk, but again the population was fairly homogenous and the anatomical location was restricted to the oropharynx. It was shown, however, that p16-ve status was associated with a higher risk of ORN; this is possibly a result of the different characteristics of the two populations such as age and risk factors, as well as treatment protocols that this study was not powered enough to identify.

**Health-related Quality of Life**

This study is the first to investigate quality of life of head and neck cancer patients in regards to their dental extractions. In addition to increasing the risk of ORN, dental extractions have not been shown to be associated with an improved health-related quality of life. Greater than 8 pre-radiotherapy dental extractions were shown to be associated with a statistically significant reduced quality of life, as were pre-radiotherapy full clearances and the development of ORN. No timing or number of dental extractions was shown to be associated with a statistically significant improved quality of life compared to no dental extractions.

The OHIP-14 and FACT H&N did not find an association between age and quality of life, however the population studied had a small age range. Female gender was associated with a lower quality of life on both dimensions, and specifically related to emotional wellbeing. Tumour location and treatment was not associated with a statistically significant difference in quality of life, however this was largely restricted by inclusion criteria. P16-negative cases were associated with a worsened quality of life; this is probably due to the inherent differences in these populations that were not able to be captured by this study. Smoking status was associated with reduced quality of life in a graded fashion with current smokers recording worse scores than ex-smokers and non-smokers respectively, and this was shown to be in a number of domains, such as physical, social, emotional and functional well-being. Development of osteoradionecrosis was predictably associated with a worse quality of life.

Excellent dental hygiene was shown to be associated with a statistically significant higher quality of life.

**Further Research**

This study has shown that any extraction confers a risk of ORN when compared to no extractions. On this basis prophylactic extractions should not be performed, and the teeth should be maintained as best as possible. However, the dental needs of head and neck cancer patients are high and frequently patients present needing dental extractions regardless of any planned radiotherapy. In these cases the only factors that can be manipulated are the extraction technique, use of adjuvant therapies such as HBO and the extraction timing. Pre-radiotherapy extractions have a limited lead time owing to the cancer diagnosis and necessary for prompt delivery of radiotherapy, however there are currently no randomised controlled trials regarding best timing of necessary dental extractions and osteoradionecrosis.

Further research in terms of improving quality of life in cancer survivors should be undertaken to confirm the finding that remaining dentate results in improved quality of life and whether or not prosthodontic rehabilitation can restore the deficit caused by the edentulous state.

**Final Comments**

This thesis has shown two important points, firstly that pre-radiotherapy dental extractions do not appear to reduce the risk of developing ORN, and secondly, that pre-radiotherapy dental extractions do not appears to improve post-treatment quality of life. It is a reasonable conclusion that the practice of removing teeth as prophylaxis prior to radiotherapy be highly questioned.

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